REMARKS

By way of the present amendments, claims 1-3, 8-9, 13, 15-16 and 18-40 have been canceled without prejudice to or disclaimer of the underlying subject matter. No new matter enters through the cancellation of these claims. Therefore, claims 4-7, 10-12, 14 and 17 are pending in the present application.

1. Election/Restrictions

In the Office Action, the Examiner states that "claims 18-40 are withdrawn from further consideration as being directed to a non-elected species." The Examiner indicates that Applicants constructively elected the invention as claimed in the originally presented invention because the Applicants have "received an action on the merits for the originally presented invention." The Examiner asserts that claims 18-40 are independent or distinct because "a different active ingredient is used in the treatment." Office Action at page 2. Applicants respectfully traverse the constructive election.

All of the claims presented in the Preliminary Amendment filed September 22, 2003 involve methods of treating patients suffering from diabetic cardiomyopathy. As such, Applicants submit that a complete examination of the application would be handled most expeditiously by treating all of the pending claims as a single entity. As Section 803 of the MPEP directs, "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions." Applicants respectfully submit

that the Examiner has not suggested that a search and examination of the entire application would cause a serious burden.

Based upon the foregoing, Applicants submit that the constructive election is improper and therefore should be withdrawn. However, to facilitate prosecution, Applicants have canceled claims 18-40 without prejudice to or disclaimer of the underlying subject matter.

Further, in the Office Action the Examiner alleges that the present application contains claims directed to patentably distinct species. Office Action at page 2. Claim 4 is indicated to be generic. The alleged species are stated to be: "the many different species of GLP-1. Namely the species in claims 17-19." Applicants respectfully traverse the Species Election Requirement, and provisionally elect species GLP-1(7-36)NH_2 for further prosecution. However, it is noted that upon allowance of a generic claim, dependent claims to additional species will be considered.

Applicants submit that although each species is distinct, again, a complete examination would be handled most expeditiously by examining all of the species together. As the claims are directed to methods of treating a patient suffering from diabetic cardiomyopathy, Applicants respectfully submit that examination of all species of the application would not cause a serious burden.

For at least the foregoing reasons, Applicants submit that the Species Election Requirement is improper and therefore should be withdrawn. However, as stated above, Applicants have provisionally elected, with traverse, GLP-1(7-36)NH_2 for prosecution on the merits.

2. Rejections Under 35 U.S.C. § 103

a. Rejection Under 35 U.S.C. § 103(a) Over Aspnes et al. or DuBois in view of Horikawa et al.

Claims 4-7 10-12, 14 and 17 stand rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Aspnes *et al.* (U.S. Patent No. 6,441,015) or Du Bois (U.S. Patent No. 6,399,601) in view of Horikawa *et al.* (U.S. Patent No. 6,235,481). Applicants respectfully disagree and traverse this rejection.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There must also be a reasonable expectation of success. *See* M.P.E.P. §§2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Applicants submit that the Examiner has failed to present even a *prima facie* case of obviousness. The Examiner alleges that "Aspnes and DuBois both establish that GLP-1 (7-36) amide is know [sic] to be used to treat diabetes," and that Horikawa establishes "that diabetic patients often experience conditions such as cardiomyopathy." The Examiner concludes that "it is well within the purview of the skilled artisan to treat a patient who has diabetic cardiomyopathy since GLP-1(7-36) amide is know [sic] to be

used to treat diabetes and diabetic patients are known to experience cardiomyopathy." Office Action at page 4. Whatever else Aspnes, DuBois and Horikawa disclose, they do not teach or suggest a method of treating a patient suffering from diabetic cardiomyopathy comprising administering an effective amount of GLP-1, GLP-1 analogs, or GLP-1-like peptides. The Examiner has not pointed to any specific suggestion in any of the cited references that would lead one skilled in the art to conclude that all agents that treat diabetes would necessarily treat diabetic cardiomyopathy. It is impermissible hindsight to find it obvious for one skilled in the art to combine the various prior art references to reach the invention in the present application absent some suggestion or motivation in the prior art. Therefore, it would not be obvious to one of skill in the art, from reading Aspnes *et al.*, Du Bois, and Horikawa *et al.*, that one could treat diabetic cardiomyopathy using GLP-1.

Moreover, the cited references provide no reasonable expectation of success. Not all agents useful for treating diabetes would necessarily treat conditions associated with diabetes, such as diabetic cardiomyopathy, once they have occurred. In fact, there is a continuing need for treatments of diabetic cardiomyopathy, despite known diabetic therapies. *See, e.g.*, Cai *et al.*, "Oxidative stress and diabetic cardiomyopathy: a brief review," *Cardiovasc. Toxicol. 1(3)*:181-193 (2001). Furthermore, it has recently been noted that it is unclear whether metabolic control will influence diabetic heart failure. *See, e.g.* Bauters, *et al.*, "Influence of diabetes mellitus on heart failure risk and outcome," *Cardiovascular Diabetology* 2:1 (2003) (attached hereto). As such, the skilled artisan would have no reasonable expectation of success in light of the cited references.

Accordingly, for at least these reasons, the rejection under 35 U.S.C. § 103(a) of Aspenes *et al.* or DuBois in view of Horikawa *et al.* is improper. Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

b. Rejection Under 35 U.S.C. § 103(a) Over Efendic in View of Horikawa

Claims 4-7, 10-12, 14 and 17 have been rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Efendic (U.S. Patent No. 6,277,819) in view of Horikawa *et al.* For at least the reasons set forth below, withdrawal of this rejection is believed to be in order.

The Examiner purports that Efendic discloses treating diabetes with GLP-1(7-36) and that "diabetic patients often experience diabetic cardiomyopathy." Office Action at page 5. The Examiner purports that Horikawa *et al.* discloses conditions associated with diabetes, including cardiomyopathy.

Neither of these references, either alone or taken together, disclose or suggest a method of treating a patient suffering from diabetic cardiomyopathy, comprising administering a therapeutically effective amount of GLP-1, GLP-1 analogs, GLP-1-like peptides. As discussed above, the Examiner has used impermissible hindsight to combine these references to find the present claims obvious.

Moreover, as argued above, not all therapies useful for treating diabetes would necessarily treat conditions associated with diabetes, such as diabetic cardiomyopathy, once they have occurred. *See*, again, the Cai *et al.* article, in which it is made clear that treatments for diabetic cardiomyopathy are needed (despite the advances in the discovery

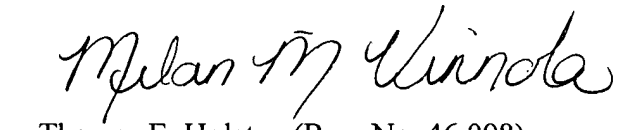
of treatments for diabetes). Therefore, it would not be obvious to one of skill in the art, from reading Efendic and Horikawa *et al.*, that GLP-1 would be useful in a method for treating diabetic cardiomyopathy.

In light of these remarks, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing arguments and amendments, each of the presently pending claims is believed to be in immediate condition for allowance. All of the stated grounds of rejection have been traversed, accommodated, or rendered moot. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue. The Examiner is encouraged to contact the undersigned at 202.942.5085 should any additional information be necessary for allowance.

Respectfully submitted,



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Influence of diabetes mellitus on heart failure risk and outcome

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Abstract

Our aim is to summarize and discuss the recent literature linking diabetes mellitus with heart failure, and to address the issue of the optimal treatment for diabetic patients with heart failure.

The studies linking diabetes mellitus (DM) with heart failure (HF): The prevalence of diabetes mellitus in heart failure populations is close to 20% compared with 4 to 6% in control populations. Epidemiological studies have demonstrated an increased risk of heart failure in diabetics; moreover, in diabetic populations, poor glycemic control has been associated with an increased risk of heart failure. Various mechanisms may link diabetes mellitus to heart failure: firstly, associated comorbidities such as hypertension may play a role; secondly, diabetes accelerates the development of coronary atherosclerosis; thirdly, experimental and clinical studies support the existence of a specific diabetic cardiomyopathy related to microangiopathy, metabolic factors or myocardial fibrosis. Subgroup analyses of randomized trials demonstrate that diabetes is also an important prognostic factor in heart failure. In addition, it has been suggested that the deleterious impact of diabetes may be especially marked in patients with ischemic cardiomyopathy.

Treatment of heart failure in diabetic patients: The knowledge of the diabetic status may help to define the optimal therapeutic strategy for heart failure patients. Cornerstone treatments such as ACE inhibitors or beta-blockers appear to be uniformly beneficial in diabetic and non diabetic populations. However, in ischemic cardiomyopathy, the choice of the revascularization technique may differ according to diabetic status. Finally, clinical studies are needed to determine whether improved metabolic control might favorably influence the outcome of diabetic heart failure patients.

Background

Heart failure (HF) is a major and growing public health issue. It is estimated that approximately 4 to 5 million Americans have HF, and that an additional 400,000 patients are diagnosed with HF each year [1]. HF prevalence is expected to reach 10 million cases in the U.S. by the year 2007 [2].

In spite of significant advances in management and treatment, the mortality of patients with HF remains high. In the CIBIS II (Cardiac Insufficiency Bisoprolol Study II) trial, after a median follow-up of 15 months, the all cause mortality was 11.8% in the group of patients receiving the beta-blocker bisoprolol [3]. In the ATLAS (Assessment of Treatment with Lisinopril And Survival) trial, after a me-

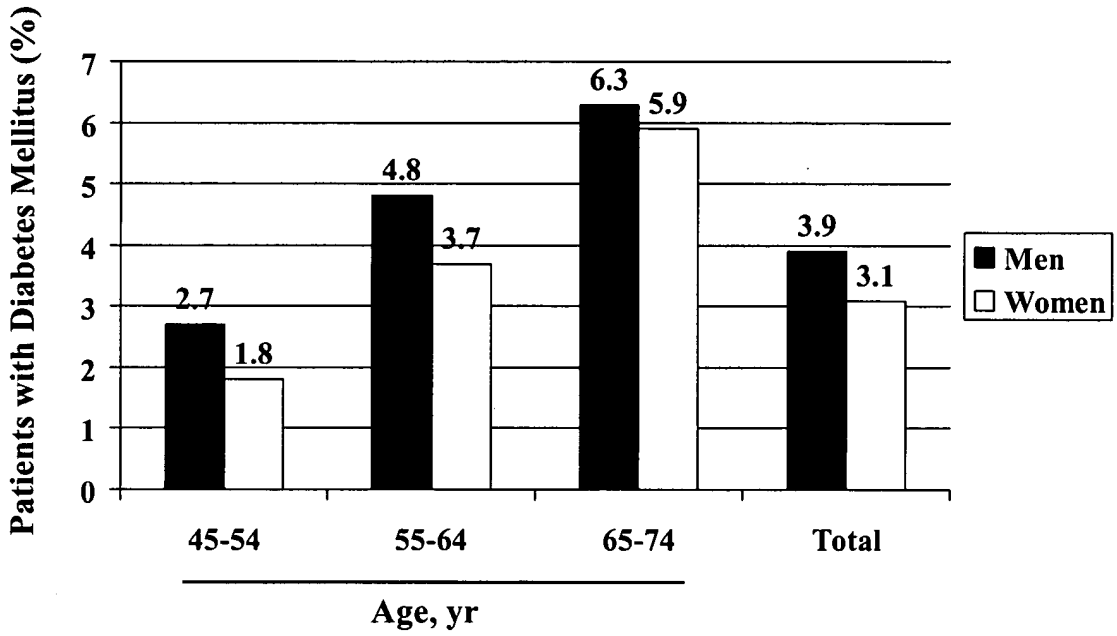

Figure 1
Prevalence of diabetes mellitus in an unselected population. This figure shows the prevalence of diabetes mellitus stratified by sex and age in the Framingham cohort. A higher proportion of diabetics is observed in subjects aged over 65 years. Adapted from reference [11].

dian follow-up of 46 months, the all cause mortality was 42% in the group of patients randomized to high dose of the angiotensin converting enzyme (ACE) inhibitor lisinopril [4]. In unselected populations, the outcome is even worse. Data from the Medicare population demonstrated a 6-year mortality rate in HF patients of 84% in men and 77% in women [5]. In the EPICAL (Epidémiologie de l'Insuffisance Cardiaque Avancée en Lorraine) observational study, the all cause one-year mortality was 35.4% [6].

HF is also a major cause of morbidity; chronic HF results in almost 1 million hospitalizations each year in the U.S. [7]. This has a major impact on health care expenditure. In 1991, the total inpatient and outpatient costs for HF were estimated to be $38 billion (5.4% of the health care budget that year) [8]. As the population ages and the number of patients with HF increases, the economic burden of HF will inevitably increase [9].

Over recent years, the prevalence of diabetes mellitus (DM), in particular type II diabetes, has increased significantly. The prevalence of DM in adults worldwide was estimated to be 4% in 1995 and is projected to rise to 5.4% by the year 2025 [10]. In developed countries, the prevalence of DM is higher in the elderly (over 65 years) population [11] (Figure 1). DM is a well known and important risk factor for cardiac disease [12–15].

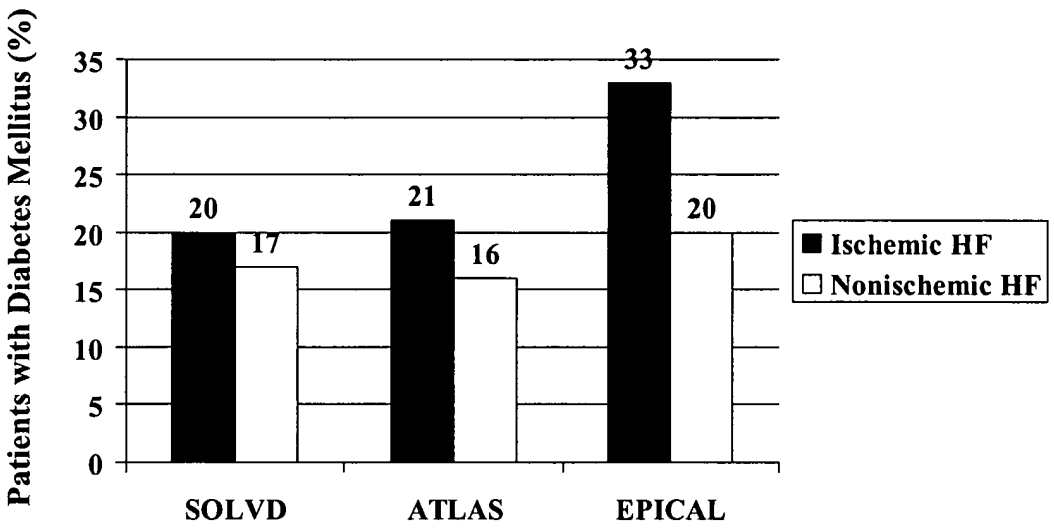

Figure 2
Prevalence of diabetes mellitus in HF populations according to HF etiology. This figure shows the prevalence of diabetes mellitus in 3 different populations [6,18,27]. A high proportion of diabetics was observed in all 3 studies.

While the most common cardiac manifestation in diabetic patients is coronary artery disease, DM also appears to be strongly linked to HF. Approximately 15 to 25% of patients with HF are diabetics [6,16–18] and it has been suggested that DM may play an important role in the pathogenesis, prognosis, and response to treatment of HF [19]. In addition, advanced HF is related to marked insulin resistance [20]. The aim of this paper will be to summarize and discuss the available literature linking DM with HF, and to address the issue of the optimal treatment for diabetic patients with HF.

The studies linking DM with HF

The epidemiological evidence linking DM with HF

As shown by subgroup analyses of randomized studies, a significant proportion of patients with HF are diabetics (Figure 2). In the SOLVD (Studies of Left Ventricular Dysfunction) clinical trials, 15% of patients were diabetic in the Prevention arm and 26% in the Treatment arm [17]. In the V-HeFT II (Vasodilator Heart Failure Trial II), the proportion of patients with DM was 20% [16]. More recently, Ryden et al reported the results of the ATLAS study in patients with and without DM: of the 3164 patients included in the study, 611 (19%) were taking hypoglycemic agents (oral or insulin) at baseline and were considered as having clinical DM [18]. Information on the prevalence of DM in HF populations can also be obtained from registries; the unselected nature of the patients consecutively included in registries may provide a better estimate of the true rate of DM in patients with HF. The SOLVD Registry was conducted in conjunction with the Prevention and the Treatment trials and enrolled a large cohort of patients with an ejection fraction <45% to determine the baseline characteristics of a population with left ventricular dys-

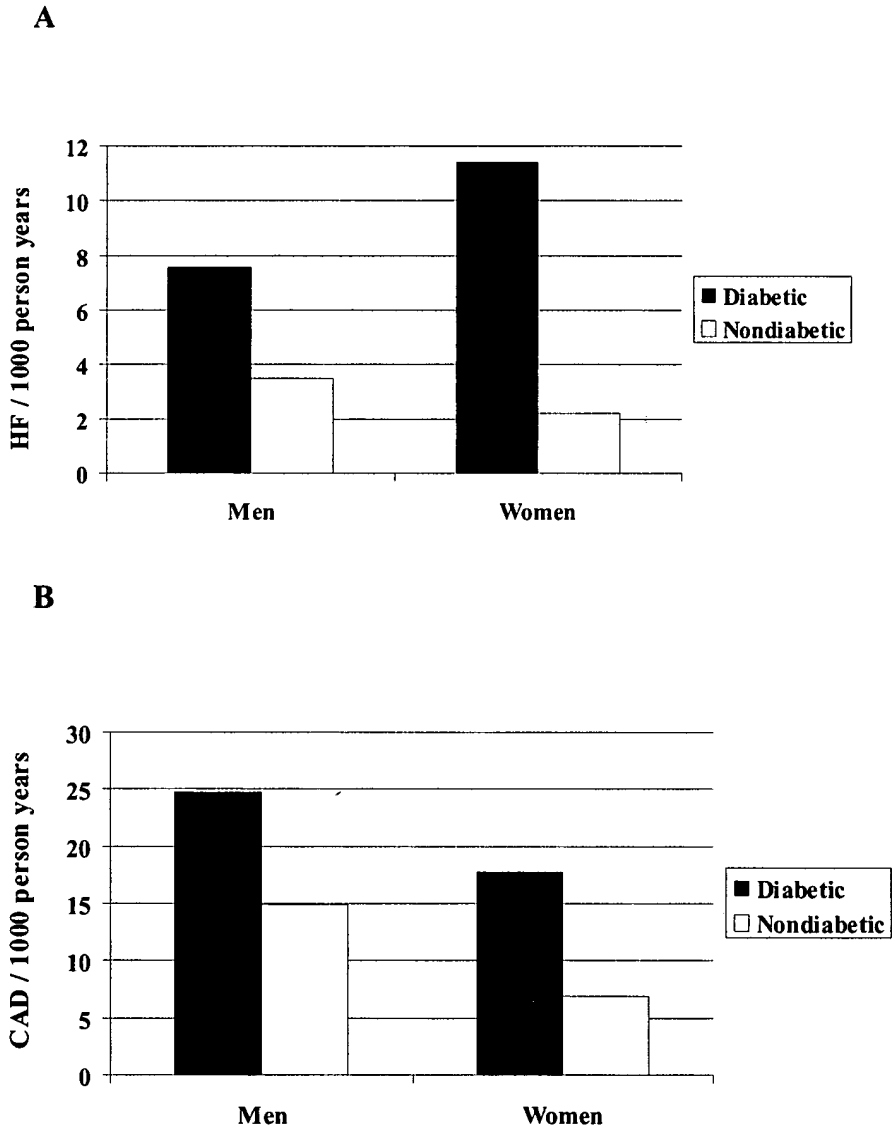

Figure 3
Incidence of HF and coronary artery disease (CAD) as a function of diabetes mellitus in general populations. The rates of both HF (Fig 3A) and CAD (Fig 3B) are higher in diabetics. The relative risks are higher for women than for men. Adapted from reference [11].

function. A total of 6076 patients with left ventricular dysfunction were included in the SOLVD Registry; among these, 1425 (23%) were classified as diabetics by the investigators [17]. In the EPICAL study [6], a registry of consecutive patients hospitalized for advanced chronic HF due to left ventricular systolic dysfunction (ejection fraction <30%), 26% of patients had an history of type I or type II DM. Overall, the rate of DM in HF populations is thus close to 20%. This rate is much higher than the 4 to 6% prevalence of DM observed in age-matched control populations [10,11] (Figure 1).

The first demonstration of an increased risk of HF in patients with DM was reported by Kannel and McGee [11] based on data obtained from 20 years follow-up of the Framingham cohort. The incidence of HF according to sex and diabetic status is shown in Figure 3A; an increased risk of HF was observed in patients with DM. Compared with non-diabetic males and females, the age-adjusted relative risks of HF for diabetic males and females were 2.20 and 5.37, respectively [11]. In a study by Tenenbaum et al in patients with ischemic heart disease, the incidence of HF at 6 to 9-year follow-up was 35.7% in non diabetic patients, 39% in patients with impaired fasting glucose and 45.7% in diabetic patients [21]. Other studies have demonstrated that the incidence of HF in diabetic patients is significantly correlated with HbA1c levels. This was primarily shown in the UK Prospective Diabetes Study (UKPDS) [22] (Figure 4A). These results were confirmed in a large population-based sample of 48,858 diabetic patients [23]; after adjustment for age and sex, each 1% increase in HbA1c was associated with a 12% increased risk of hospitalization for HF and/or death. These data demonstrating a strong association between HbA1c levels and HF in diabetic populations should be interpretated with caution; although poor glycemic control may be an independent risk factor for developing HF in diabetic populations, it is also conceivable that these data simply suggest a longer duration of DM, which is difficult to control, and therefore the development of HF may be more closely related to the duration of DM than to glycemic control.

Finally, although our aim was to review studies analyzing the risk of HF as a function of diabetic status, it must also be acknowledged that HF may predict future DM development; this has been demonstrated in an elderly population by Amato et al [24].

The mechanisms of HF in diabetic patients

DM may be causally related to HF development by at least 3 mechanisms: due to associated comorbidities, by favoring the development of coronary atherosclerosis, or through a specific diabetic cardiomyopathy.

Associated comorbidities or risk factors may partly account for the increased risk of HF in diabetic patients. These cardiovascular risk factors such as dyslipidaemia, hypertension, hypercoagulability, obesity and inflammation are part of the insulin resistance syndrome and are, at least partly, regulated by nuclear peroxisome proliferator-activated receptors (PPARs); activation of PPAR-gamma improve insulin sensitivity and endothelial function, and lower inflammation and blood pressure [25]. In the Framingham cohort, diabetic men and women had higher blood pressures and were more obese than non-diabetics; diabetic women had, in addition, higher LDL-cholesterol values; HDL-cholesterol values were consistently lower in those with DM than in those without DM in both sexes [26]. The same observation has been reported in HF populations: In the SOLVD trials [17,27], for example, diabetic patients were older and were more likely to have a history of hypertension than non-diabetic patients: in the treatment arm, 54% of diabetics had hypertension versus 38% of non-diabetics ($p < 0.001$); in the prevention arm, 53% of diabetics had hypertension versus 34% of non-diabetics ($p < 0.001$). Although this may in part explain the higher incidence of HF in diabetic patients, other mechanisms must also play a role. Indeed, in most of the studies discussed previously, diabetes or poor glycemic control remained significantly associated with HF after adjustment for important baseline clinical variables including age, sex, and hypertension [11,22,23].

The increased risk of atherosclerosis in diabetic patients may also contribute significantly to the increased risk of HF. Coronary artery disease is the underlying cause of HF in approximately two thirds of patients with left ventricular systolic dysfunction [28]. DM is associated with a markedly increased risk of coronary artery disease. In the Framingham study, the incidence of coronary artery disease was increased in diabetic subjects (Figure 3B). In UKPDS, the risk of myocardial infarction increased as a function of HbA1c levels [22] (Figure 4B). In the study by Haffner et al [29], the seven-year incidence rate of myocardial infarction in diabetic subjects without prior myocardial infarction at baseline was 20.2% versus only 3.5% in non-diabetic subjects without prior myocardial infarction at baseline (Figure 5). This increased risk of atherosclerosis in diabetic subjects has been attributed to diverse mechanisms such as endothelial dysfunction [30] or altered hemostatic factors (higher levels of fibrinogen [31], plasminogen activator-inhibitor-1 [32,33] or VonWillebrand factor [34]), or altered platelet function [35–38]). Molecular mechanisms linking hyperglycemia and atherosclerosis have been recently reviewed by Aronson et al [39].

There are also data to suggest that DM may predispose to HF development through the existence of a specific dia-

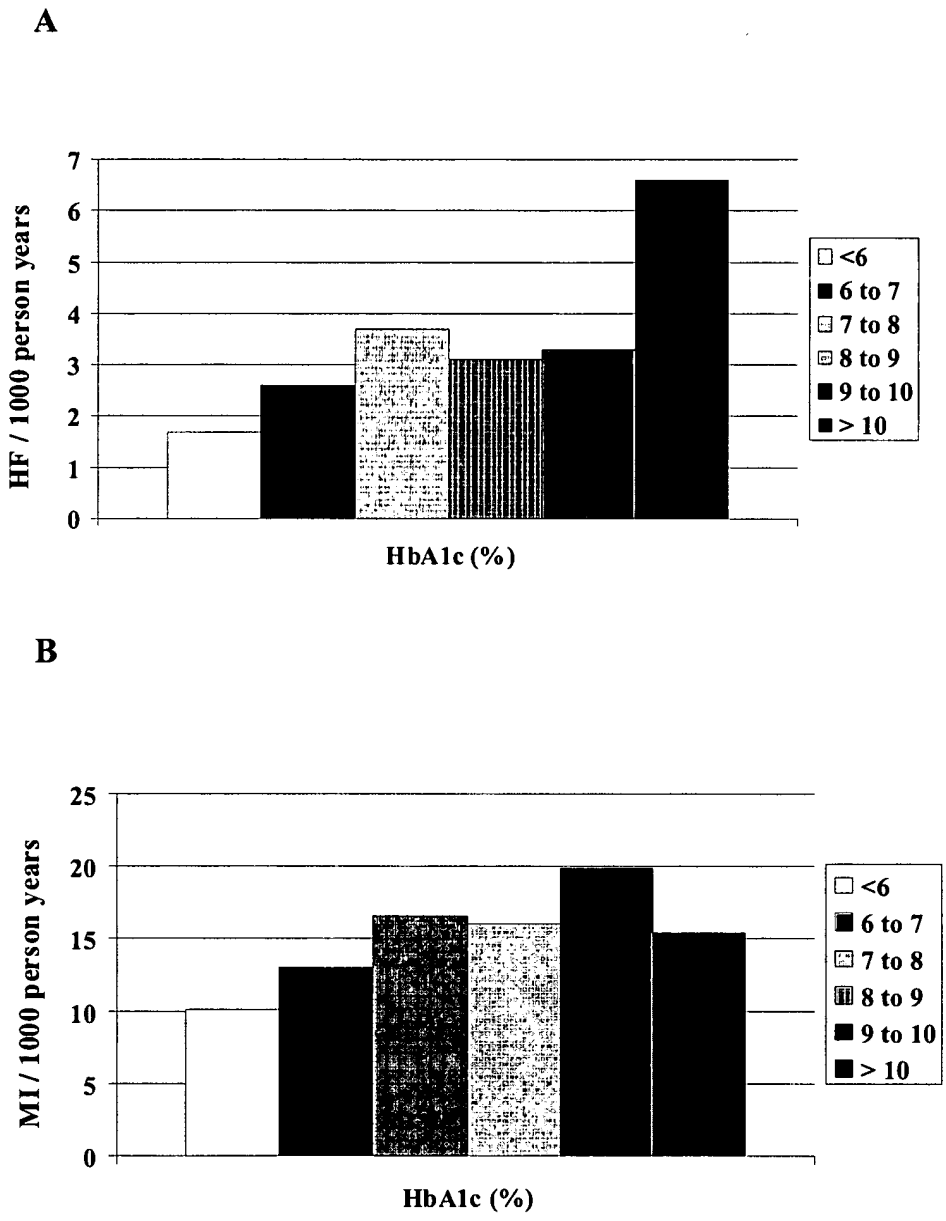

Figure 4
Incidence of HF and myocardial infarction (MI) as a function of glycemic control in diabetic populations. The incidence of both HF (Fig 4A) and MI (Fig 4B) was positively correlated with HbA1c levels. Adapted from reference [22].

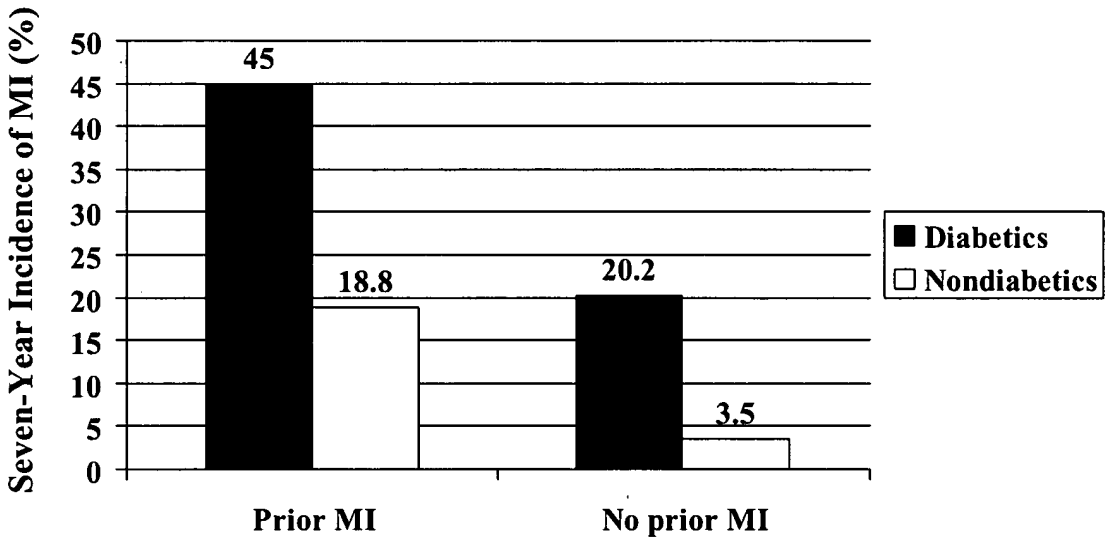

Figure 5
Incidence of MI in diabetic versus nondiabetic populations. The 7-year incidence of MI is much higher in diabetics than in nondiabetics. This holds true for patients with or without prior MI. The risk of MI in diabetics without prior MI is similar to that observed in nondiabetics with prior MI. Adapted from reference [29].

betic cardiomyopathy [40]. The exact mechanism(s) by which DM may induce HF independent of epicardial coronary artery disease is (are) unknown but several hypotheses have been advanced; these include microangiopathy, metabolic factors, and fibrosis. Intramyocardial microangiopathy has also been observed in diabetic hearts [41–43]; combined with functional abnormalities related to endothelial dysfunction, diabetic microangiopathy may explain the reduced coronary blood flow reserve observed in diabetic patients [30,44,45]. Metabolic factors may also play a role in the development of myocardial dysfunction; hyperglycemia, impaired myocardial glucose uptake, and increased turnover of free fatty acids may all contribute to DM-related myocardial dysfunction (for review see [46–48]. Finally, experimental and clinical data also point to a potential role for myocardial fibrosis in diabetic cardiomyopathy; intramyocardial accumulation of collagen is a well-demonstrated consequence of DM [49,50]; moreover, the deposition of advanced glycation end products (AGEs) may result in increased left ventricular stiffness and consequently to diastolic dysfunction [51–53]. In summary, various mechanisms may induce a specific diabetic cardiomyopathy. Whether this diabetic cardiomyopathy alone may cause HF is however unknown; another possibility is that these myocardial alterations related to DM may predispose to the development of HF in response to other insults such as coronary artery disease or hypertension (Figure 6). After an acute myocardial infarction,

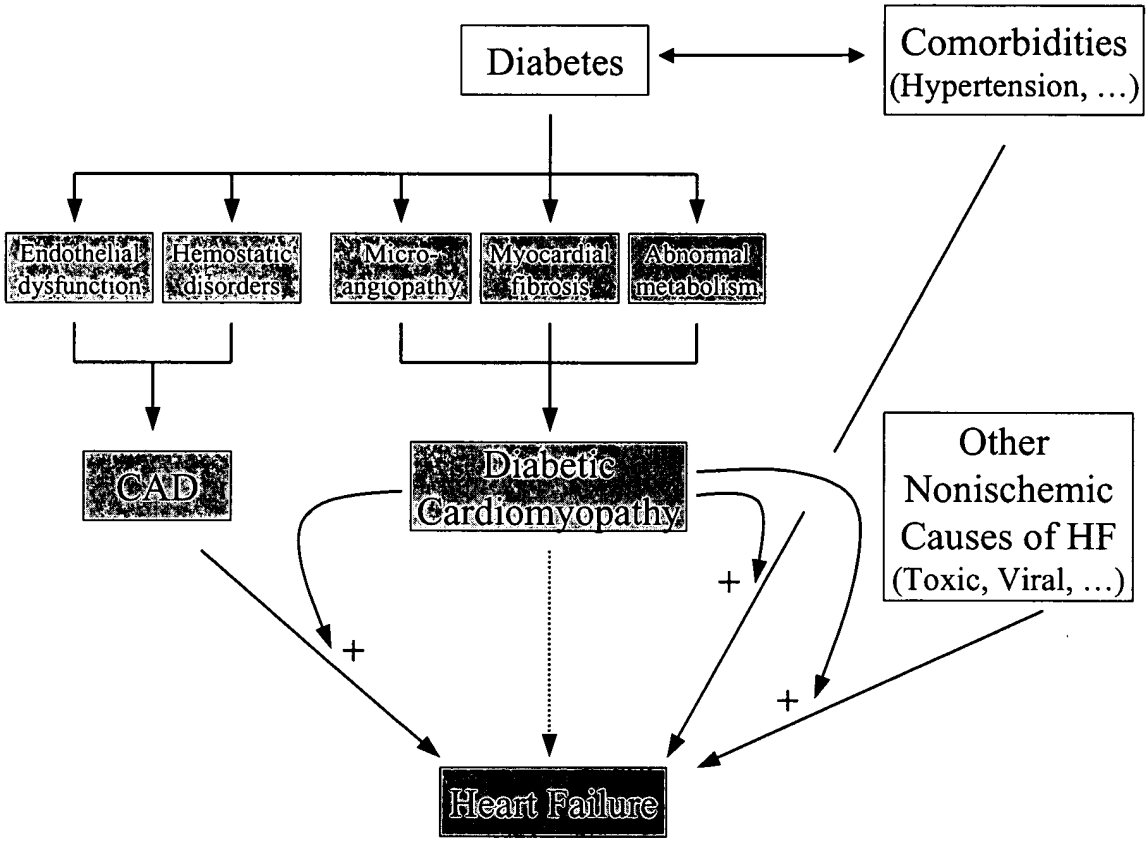

Figure 6

Potential mechanisms linking diabetes mellitus to heart failure. Diabetes mellitus is associated with multiple physiopathological changes in the cardiovascular system. Among these, endothelial dysfunction and hemostatic disorders may at least in part account for the higher risk of coronary artery disease (CAD) while microangiopathy, myocardial fibrosis, and abnormal myocardial metabolism have been implicated in the pathogenesis of a specific diabetic cardiomyopathy. When it occurs in diabetic patients, heart failure (HF) is, in most cases, a consequence of CAD; other possible causes include the comorbidities frequently encountered in diabetic patients such as hypertension, or other causes of nonischemic cardiomyopathy. The existence of a diabetic cardiomyopathy may increase the risk of HF in response to these insults; however, whether diabetic cardiomyopathy alone may be responsible for HF remains unknown.

decreased compensatory responses of non-infarcted area have been described in diabetic patients [54–56]. Similarly, a synergistic effect may exist between DM and hypertension for the development of myocardial fibrosis [57].

Determining diabetic status: an additional prognostic indicator in heart failure patients?

Risk stratification is an important step in the management of patients with HF; high risk patients may indeed benefit from more aggressive therapeutic strategies. Parameters such as New York Heart Association (NHYA) class, maximal VO2, left and right ventricular ejection fraction have been identified as powerful predictors of clinical outcome in HF patients [58–62].

The first suggestion that DM may be a predictor of poor clinical outcome in HF patients came in a report from Shindler et al [17]. A subgroup analysis of the SOLVD trials (combining the Prevention and the Treatment trials), showed that both all cause mortality and cardiovascular mortality at a mean follow-up of 3 years were significantly higher in diabetic patients than in non-diabetic patients (Figure 7). Multivariate analysis was used to assess the significance of DM as an independent predictor of outcome.

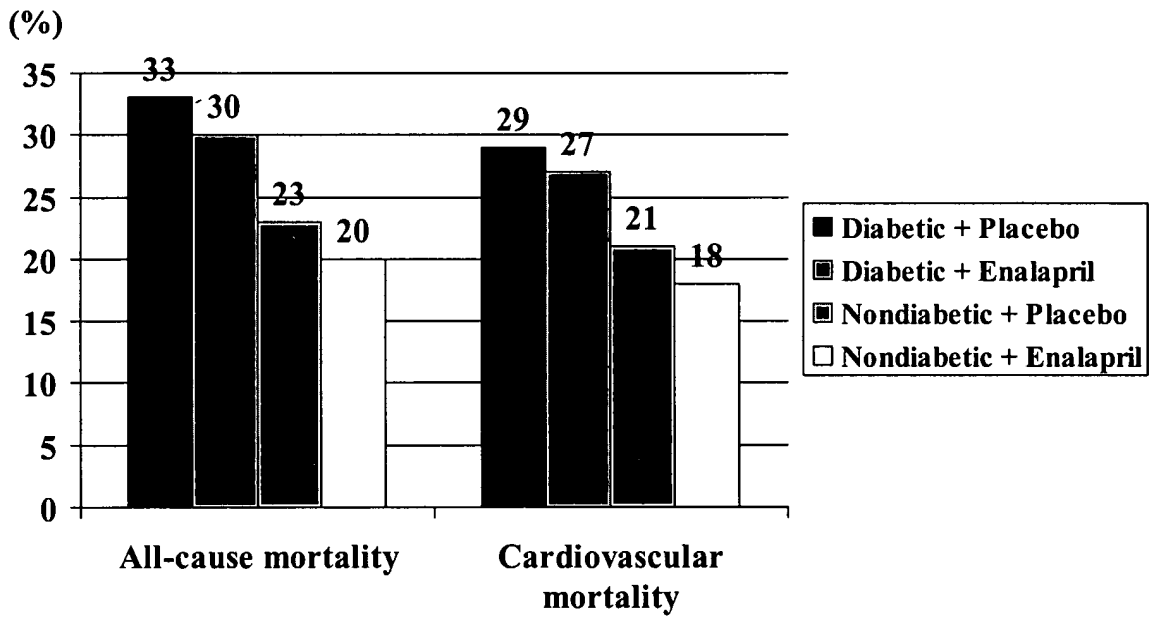

Figure 7
Diabetes mellitus as a predictor of clinical outcome in HF populations. All cause mortality and cardiovascular mortality are higher in diabetics than in nondiabetics. Adapted from the SOLVD trials [17].

After adjusting for important baseline variables such as age, sex, NYHA classification, or left ventricular ejection fraction, DM remained a significant predictor of clinical outcome in both the Prevention and the Treatment trials. More recently, Dries et al reanalyzed the SOLVD database to determine whether DM would have a different impact on clinical outcome in ischemic versus non-ischemic HF [27]. After adjustment for baseline variables, they found that DM was associated with an increased risk for all-cause mortality in patients with ischemic HF (RR 1.37, 95% CI 1.21 to 1.55), but not in patients with non-ischemic HF (RR 0.98, 95% CI 0.76 to 1.32) (Figure 8). Moreover, they suggested that the increased mortality in patients with ischemic HF compared with non-ischemic HF (reviewed in [63]) may be limited to the diabetic subgroup. If these findings are confirmed in independent studies, at least two explanations may account for the negative interaction between DM and the ischemic etiology of heart failure. Firstly, diabetic HF patients may have a higher risk of coronary plaque rupture and thrombosis [29,64]; recurrent myocardial infarction is a major cause of death in patients with ischemic HF [65]; in addition, non fatal myocardial infarction may further deteriorate left ventricular function in patients with ischemic HF. Furthermore, the presence of various components of a specific diabetic cardiomyopathy such as impaired myocardial glucose uptake may be especially deleterious in patients with ischemic HF [66–69].

The links between DM and HF: the need for new studies

Most of the data on HF in diabetics summarized above have been obtained from post-hoc analysis of randomized studies or registries and as such should be interpreted with caution. In the SOLVD trial for example, the

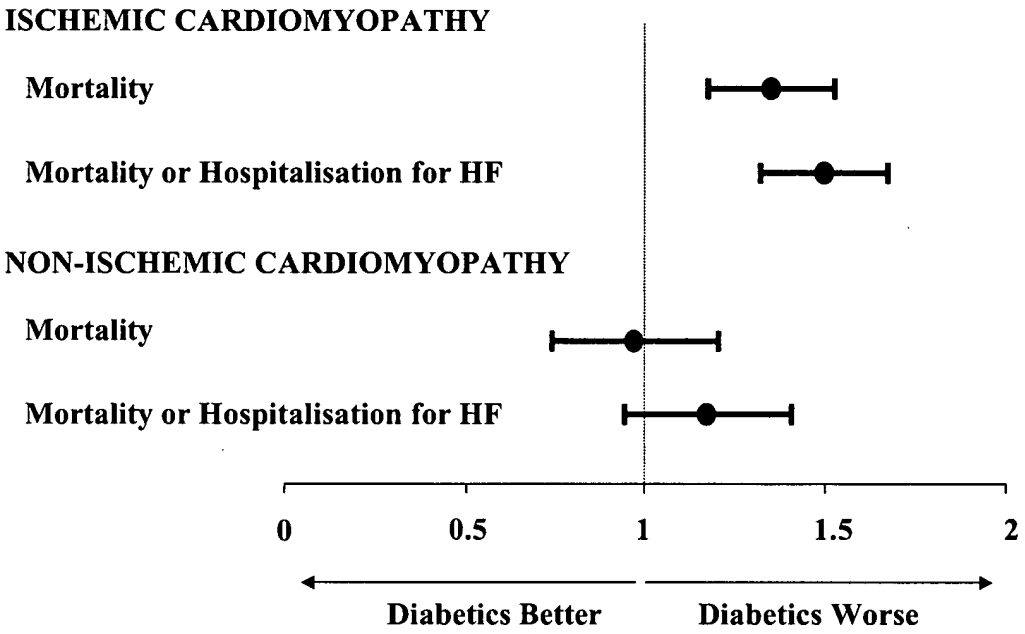

Figure 8
Prognostic impact of diabetes mellitus according to HF etiology. Subgroup analysis of the SOLVD trials. The deleterious impact of diabetes mellitus is limited to the ischemic subgroup. Adapted from reference [27].

diagnosis of DM was solely based on self-reporting by the patient or on documentation in the patient's medical records and data on the duration of DM, severity of DM, and medications used to treat DM were not available. Similarly, in SOLVD, the definition of the etiology of HF (i.e., ischemic versus non ischemic) was based on the judgement of the investigators at the participating sites after reviewing all available information and did not routinely include cardiac catheterization or non-invasive testing.

New studies in HF populations with careful and prospective characterization of diabetic patients are needed; these studies may be designed either as ancillary studies of prospective randomized trials or as part of prospective registries on HF. The variables recorded should provide information on DM type and duration, and antidiabetic management (diet alone, oral hypoglycemic drugs, insulin). The presence/absence of signs of end-organ damage (retinopathy, neuropathy, nephropathy) would be a useful indicator of DM severity and duration and should also be recorded. Important biological variables related to the presence of DM or its complications (glycemia, HbA1c, serum creatinine, albuminuria, etc.) should also be prospectively determined. Finally, in view of the potential interactions between DM and CAD on HF risk and outcome, special attention should be given to prospective character-

ization of HF etiology (i.e., ischemic versus non ischemic).

Such studies would provide information on the characteristics of the diabetic cohort in HF populations and on the relationship between CAD and HF in diabetics. In addition, when coupled with clinical follow-up, these studies would allow propective confirmation of the hypothesis that DM has a deleterious impact on prognosis in HF patients and could determine whether biological markers such as HbA1c may serve as prognostic indicators in HF patients.

Treatment of HF in diabetic patients

Medical treatment

Post-hoc analyses of large randomized studies have shown that the beneficial effect of conventional HF treatment is maintained in the subgroup of diabetic patients. This has been conclusively demonstrated for the two classes of drugs, regarded as cornerstone treatments, namely ACE inhibitors and beta-blockers. In the SOLVD prevention and Treatment trials [70,71], patients were randomized to either placebo or the ACE inhibitor enalapril; the efficacy was similar in diabetic and non-diabetic patients (Figure 7). There was no interaction between diabetic status and drug assignement with respect to the study endpoints [17]. In the ATLAS trial [4], patients were randomized to high or low doses lisinopril. The relative risk reduction in mortality for high-dose vs low-dose lisinopril was 14% for patients with diabetes mellitus and 6% for those without [18]; high-dose lisinopril was as effective in reducing hospitalizations for heart failure in diabetics as in non-diabetics (21% vs 24%) [18]. In ACE inhibitor-intolerant HF patients, the available literature supports the use of angiotensin II blockers [72]. In the CIBIS II trial, patients were randomized to placebo or the beta-blocker bisoprolol [3]; the efficacy was similar in diabetic and non-diabetic patients with respect to all mortality/morbidity endpoints [73]. For example, the relative risk (bisoprolol vs placebo) for mortality was 0.81 (95% CI 0.51–1.28) in diabetics and 0.66 (95% CI 0.54–0.81) in non-diabetics; the heterogeneity test for interaction was not statistically significant. Although these results were obtained from post-hoc analyses and as such have limitations from a methodological standpoint, the well-demonstrated benefits of ACE inhibitors and beta-blockers appears to be maintained in the diabetic subgroups. In addition, a similar relative risk reduction when applied to a high risk population such as diabetic HF patients will automatically translate into a major benefit in term of reduction in the absolute number of events.

In addition to ACE inhibitors and beta-blockers, patients with ischemic HF also benefit from secondary prevention with agents demonstrated to reduce atherosclerosis progression and to diminish the rate of acute coronary events. The use of antiplatelet agents was associated with an improvement in survival in patients with symptomatic or asymptomatic left ventricular dysfunction in the SOLVD study [74]. Statin therapy has been associated with an improved outcome in patients with coronary artery disease and left ventricular dysfunction [75]; moreover, in the 4S study, administration of simvastatin reduced the occurrence of HF [76]. Although no data are available concerning diabetic patients with ischemic HF, the demonstrated benefit of antiplatelet and statin therapy in diabetic patients with coronary artery disease [77–79] clearly supports a strategy of aggressive secondary prevention in diabetic patients with ischemic HF.

The need for new strategies/studies

Besides medical treatment for HF and the optimal use of secondary prevention strategies in cases with an ischemic origin, there are still important unanswered questions that will require further studies. For many diabetic patients with ischemic HF, the decision to revascularize and the choice of the revascularization technique are key issues. Moreover, the impact of DM treatment on HF outcome also needs to be considered.

Myocardial revascularization

Patients with ischemic cardiomyopathy represent an important subset of HF patients in whom myocardial revascularization may offer the potential for reduced symptoms and enhanced prognosis [80–84]. The optimal therapeutic strategy for coronary revascularization of diabetic patients is still a matter of debate [85–90]. Limited data are available regarding the relative merits of Coronary Artery Bypass Grafting (CABG) versus Percutaneous Transluminal Coronary Angioplasty (PTCA) in diabetic patients with ischemic HF: in a recent report of the Bypass Angioplasty Revascularization Investigation (BARI) study, the 7-year mortality was compared in patients randomized to CABG or PTCA according to the presence or absence of diabetes mellitus and left ventricular dysfunction at baseline [90]. In non-diabetic patients with left ventricular dysfunction the 7-year survival was similar in the CABG group and the PTCA group; on the other hand, in diabetic patients with left ventricular dysfunction CABG was associated with a better outcome than PTCA (Figure 9). Although these results support the choice of CABG as revascularization technique for diabetic patients with left ventricular dysfunction and multivessel coronary artery disease, it must be noted that patient selection and inclusion in the BARI study was performed >10 years ago [85]. Since then, new modalities of myocardial revascularization have been developed; the generalisation of the use of arterial grafts [85] and of coronary stent implantation [91,92], and the advent of IIb/IIIa antagonists [93,94] all have the potential to improve the outcome of diabetic HF

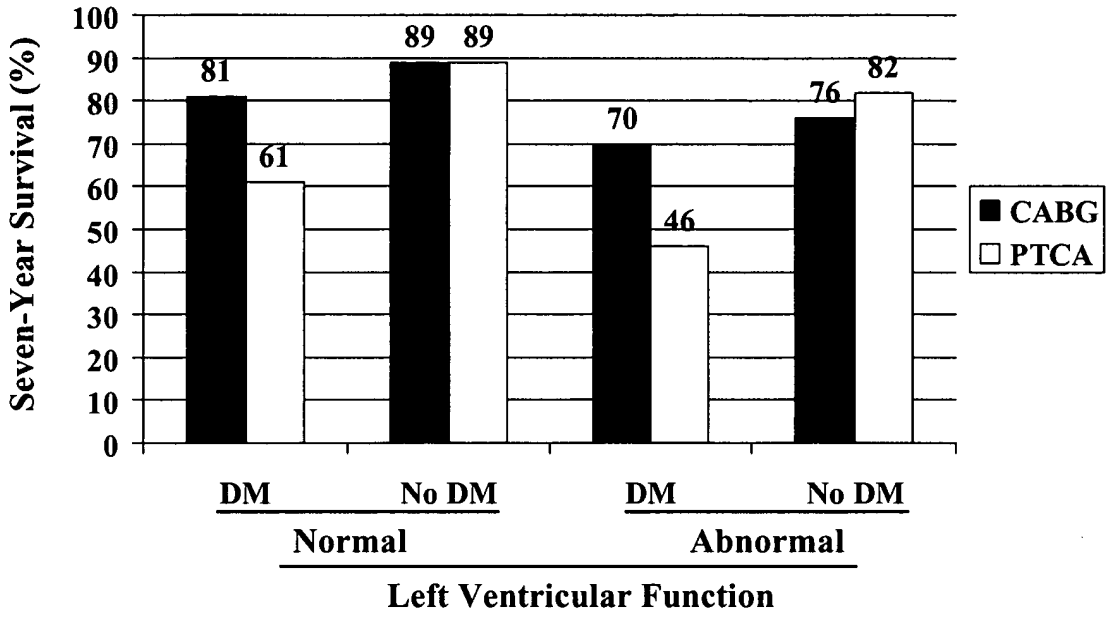

Figure 9
Survival in patients with multivessel CAD treated by CABG or PTCA according to presence/absence of diabetes mellitus and left ventricular dysfunction at baseline. Adapted from the BARI study [90]. In the diabetes mellitus (DM) subgroup, the outcome was better in the CABG group than in the PTCA group; this holds true in the presence or in the absence of left ventricular dysfunction.

patients undergoing myocardial revascularization. Similarly, the recent demonstration that drug eluting stents may significantly reduce the risk of restenosis could have a major impact in diabetic HF patients undergoing percutaneous coronary revascularization [95].

Future studies will have to clarify the role of revascularization in diabetic patients with ischemic HF. It will be important to determine if revascularization in diabetics carries any advantage over medical therapy, a question that is currently under evaluation in the BARI 2D study (although not specifically in HF patients). If it is shown that revascularization improves prognosis, it would be appropriate to aggressively exclude an ischemic origin in diabetic HF patients.

Metabolic control

The impact of DM treatment in HF patients should also be considered. At the present time, it has not been determined whether improved metabolic control might favorably influence the outcome of diabetic HF patients and large clinical studies are urgently needed to provide an answer to this important question. The need for such studies is underlined by preliminary data suggesting that strict metabolic control may reverse to some extent the consequence of diabetic cardiomyopathy [96]. Such studies

would also determine whether the preferred treatment for DM should be an insulin-sensitizing regimen or an insulin-providing regimen. Lifestyle interventions [97] (including dietary changes, increased physical activity and weigth loss) could also be specifically tested in diabetic HF patients. Finally, taking into account the possible interaction between HF etiology and the impact of metabolic control, prespecified subgroup analysis (non ischemic HF vs ischemic HF) would appear mandatory.

Conclusions

In summary, HF in diabetic patients is an important health problem. Approximately 20 to 25% of HF patients are diabetics. The review of the available literature suggests that the diabetic subgroup of HF patients deserves special consideration: at the present time, the natural history of HF in diabetic patients appears different with a higher mortality especially in the case of ischemic HF; moreover, although conventional HF treatments appear to be uniformly beneficial, in the case of ischemic HF the choice of the revascularization technique may differ according to diabetic status. Thus, an early and precise characterization of diabetic status should be encouraged not only in future clinical trials but also in everyday management of HF patients.

The present review underscores the need for new studies to help unravel the interplay between diabetes, atherosclerosis, and heart failure and to determine the specific role of currently available and novel therapies in the diabetic population.

Finally, a better understanding of the mechanisms leading to HF in diabetic patients may also help to design preventive strategies. At the present time, the well-documented beneficial effects of primary prevention of CAD in diabetics supports the preventive use of drugs such as statins [98] and ACE inhibitors [99]; other aspects such as for example careful blood pressure control [100] may also have a tremendous impact on the prevention of HF in this high risk population.

Abbreviations used

ACE, Angiotensin converting enzyme

AGEs, Advanced Glycation End products

ATLAS, Assessment of Treatment with Lisinopril and Survival trial

BARI, Bypass Angioplasty Revascularization Investigation

CABG, Coronary Artery Bypass Grafting

CIBIS II, Cardiac Insufficiency Bisoprolol Study II

DM, Diabetes Mellitus

EPICAL, Epidémiologie de l'Insuffisance Cardiaque Avancée en Lorraine

HF, Heart failure

NYHA, New York Heart Association

PTCA, Percutaneous Transluminal Coronary Angioplasty

SOLVD, Studies of Left Ventricular Dysfunction

UKPDS, UK Prospective Diabetes Study

V-HeFT II, Vasodilator Heart Failure Trial II

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